

Single cell analysis of human foetal liver captures the transcriptional profile of hepatobiliary hybrid progenitors.

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Public Summary:

Liver are essential organs for human health and is composed of hepatocytes and bile duct epithelial cells (BECs). Controversy exists regarding the cellular origin of human liver parenchymal tissue generation during embryonic development, homeostasis or repair. Capturing a human hepatic progenitor state in utero provides unparalleled and unexplored insight into the true mechanisms of human liver development. Here we report the existence of a hepatobiliary hybrid progenitor (HHyP) population in human fetal liver using single-cell RNA sequencing. HHyPs are anatomically restricted to the ductal plate of fetal liver and maintain a transcriptional profile distinct from fetal hepatocytes, mature hepatocytes and mature BECs. Our study suggests that hepatobiliary progenitor cells previously identified in mice also exist in humans, and can be distinguished from other parenchymal populations, including mature BECs, by distinct gene expression profiles. Our in depth profiling of previously undefined HHyPs finally provides an accurate template for the human liver progenitor phenotype that will be a valuable roadmap for translating ex vivo hepatic progenitor studies into successful cell-based liver disease therapies.

Scientific Abstract:

The liver parenchyma is composed of hepatocytes and bile duct epithelial cells (BECs). Controversy exists regarding the cellular origin of human liver parenchymal tissue generation during embryonic development, homeostasis or repair. Here we report the existence of a hepatobiliary hybrid progenitor (HHyP) population in human foetal liver using single-cell RNA sequencing. HHyPs are anatomically restricted to the ductal plate of foetal liver and maintain a transcriptional profile distinct from foetal hepatocytes, mature hepatocytes and mature BECs. In addition, molecular heterogeneity within the EpCAM(+) population of freshly isolated foetal and adult human liver identifies diverse gene expression signatures of hepatic and biliary lineage potential. Finally, we FACS isolate foetal HHyPs and confirm their hybrid progenitor phenotype in vivo. Our study suggests that hepatobiliary progenitor cells previously identified in mice also exist in humans, and can be distinguished from other parenchymal populations, including mature BECs, by distinct gene expression profiles.

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